Asymmetric Hofmann Elimination. Synthesis and Hofmann Degradation of Asymmetric Tertiary Amines Containing an N-Cyclooctyl Group[1a]

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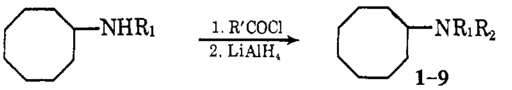
Abstract: The synthesis of a number of tertiary amines containing the N-cyclooctyl group is described. The quaternary bases derived from some of these amines were subjected to Hofmann elimination conditions. The yield of cyclooctene and ratio of *cis:trans* isomers were determined. When the other alkyl groups attached to the nitrogen atom were aliphatic, cyclooctene was formed in good yield with a preponderance of the *trans* isomer. The presence of N-benzyl and N-allyl groups on the nitrogen atom led to lower yields of cyclooctene and a predominance of the *cis* isomer.

Hofmann decomposition of fully resolved[2] N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium hydroxide was found to give a 53% yield of *cis*- and optically active *trans*-cyclooctene in a 33:67 ratio.[3] In the exploratory work in search of a quaternary base suited for the resolution and asymmetric Hofmann elimination described in the preceding paper,[3] a number of tertiary amines containing the N-cyclooctyl group were synthesized; some were converted to the methiodides and subjected to the Hofmann elimination reaction. This paper describes the results of this exploratory work.

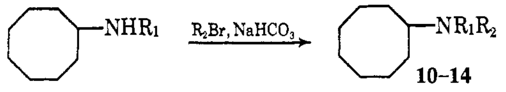
The secondary amines required as intermediates were prepared in high yield from cyclooctanone and the appropriate primary amine through the Schiff's base. The preparations were effected in separate steps because the usual low-pressure[4] and high-pressure[5] one-step reductive alkylation procedures failed to give the desired amines.

Tertiary amines **1** to **9** were prepared by acylation of the appropriate secondary amine with an acid chloride followed by reduction of the resulting amide with lithium aluminum hydride (eq 1). Tertiary amines **10** to **14** were prepared by alkylation of the secondary amine with an alkyl bromide (eq 2). The yields obtained and the properties of the amide intermediates, the amines, and their derivatives are given in Tables II, III, and IV, respectively.



1–9 (1)

	R₁	R₂
1	isobutyl	ethyl
2	isobutyl	*n*-propyl
3	isobutyl	hexahydrobenzyl
4	isobutyl	neopentyl
5	benzyl	isobutyl
6	benzyl	neopentyl
7	benzyl	CH_2-β-naphthyl
8	phenyl	benzyl
9	phenyl	neopentyl



10–14 (2)

	R₁	R₂
10	isobutyl	allyl
11	benzyl	$CH_2CO_2C_2H_5$
12	benzyl	allyl
13	benzyl	methallyl
14	phenyl	methallyl

The two least hindered amines, **1** and **2**, were readily converted to the quaternary ammonium salts on treatment with excess methyl iodide. The conversion of the other more hindered amines to their quaternary ammonium salts was effected only under more drastic conditions. For example, N-hexahydrobenzyl-N-isobutylcyclooctylamine (**3**) gave a high yield of the quaternary salt only after 3 days of heating with methyl iodide in refluxing acetonitrile. N-Benzyl-N-isobutylcyclooctylamine (**5**) gave a 71% yield of the methiodide after 26 hr under the same conditions; a shorter reaction time resulted in a lower yield, and longer reaction times resulted in a product of lower purity. N-Benzyl-N-methallylcyclooctylamine (**13**) was converted to the quaternary ammonium compound by heating in a sealed tube with methyl *p*-toluenesulfonate for 48 hr. In all, quaternary ammonium salts were prepared successfully from seven of these amines; their properties are given in Table V.

The methiodides of the other seven tertiary amines could not be prepared under the conditions investigated. Under less severe conditions, only slow formation of the hydriodide of the starting amine resulted. For example, N-benzyl-N-phenylcyclooctylamine (**8**) in methanol solution gave its hydriodide after 72 hr of heating at 70° with methyl iodide. Conditions which were rigorous enough to effect methylation were found to cause decomposition of the product; the products isolated were quaternary ammonium salts in which the labile substituents were replaced by methyl groups. For example, N-benzyl-N-neopentylcyclooctylamine (**6**) gave N-benzyl-N,N-dimethylcyclooctylammonium iodide when heated at 150° for 24 hr with excess methyl iodide.

The seven quaternary ammonium salts and also N-benzyl-N,N-dimethylcyclooctylammonium iodide

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[2] Determined by the isotopic dilution method using material enriched with nitrogen-15.

[3] A. C. Cope, W. R. Funke, and F. N. Jones, *J. Am. Chem. Soc.*, **88**, 4693 (1966).

[4] A. C. Cope and E. M. Hancock, *ibid.*, **64**, 1503 (1942).

[5] Reductive alkylation with Raney nickel as catalyst at 80° and 1000 psi for 24 hr gave a mixture of products.

Table I. Hofmann Decompositions of Quaternary Ammonium Hydroxides of the Type $C_8H_{15}\overset{+}{N}R_1R_2CH_3OH^-$

R_1	R_2	Starting amine	Total yield of cyclo-octenes, %[a]	*cis*:*trans* ratio
Methyl	Methyl		89	40:60[b]
Isobutyl	*n*-Butyl		53	33:67[c]
Isobutyl	Ethyl	**1**	7	39:61
Isobutyl	*n*-Propyl	**2**	57	32:68
Isobutyl	Hexahydro-benzyl	**3**	77	33:67
Benzyl	Isobutyl	**5**	48	86:14
Isobutyl	Allyl	**10**	21	89:11[d]
Benzyl	Allyl	**12**	0[e]	. . .
Benzyl	Methallyl	**13**	14	91.5:8.5
Benzyl	Methyl		42	87:13

[a] Over-all yield based on quaternary ammonium salt. [b] A. C. Cope, R. A. Pike, and C. F. Spencer, *J. Am. Chem. Soc.*, **75**, 3212 (1953). [c] See ref 3. [d] Other experiments gave ratios of 92:8 and 85:15. [e] Decomposition was effected by heating to 200° at 25 mm.

Table II. N-Cyclooctylamides of the Type $C_8H_{15}NR_1COR_2$

Acid chloride	R_1	R_2	Reaction time, hr	Yield, %	Bp (mm) or mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
Acetyl	Isobutyl	Methyl	1	87	102.5–104.0 (0.16)	$C_{14}H_{27}NO$	74.61	74.38	12.08	12.14	6.22	6.47
Propionyl	Isobutyl	Ethyl	2	81	117–118 (0.17)	$C_{15}H_{29}NO$	75.25	74.98	12.21	12.05	5.85	6.01
Hexahydro-benzoyl[f]	Isobutyl	Cyclohexyl	5	80[a]	144.0–146.5 (0.12)	$C_{19}H_{35}NO$	77.75	77.93	12.02	11.93	4.77	4.51
Pivaloyl[g]	Isobutyl	*t*-Butyl	2	50	113–115 (0.15)	$C_{17}H_{33}NO$	76.33	76.18	12.44	12.33	5.24	5.43
Isobutyryl	Benzyl	Isopropyl	2	87	163–166 (0.4)	$C_{19}H_{29}NO$	79.39	79.58	10.17	10.23	4.87	5.13
Pivaloyl[g]	Benzyl	*t*-Butyl	24[b]	92	150–152 (0.12)	$C_{20}H_{31}NO$	79.67	80.03	10.37	10.39	4.65	4.73
β-Naphthoyl[h]	Benzyl	β-$C_{10}H_7$	1.5	60	96.5–97.5[c]	$C_{26}H_{29}NO$	84.05	84.03	7.87	7.64	3.77	3.62
Benzoyl	Phenyl	Phenyl	24[d]	90	75–76[e]	$C_{21}H_{25}NO$	82.04	82.09	8.20	8.21	4.56	4.44
Pivaloyl[g]	Phenyl	*t*-Butyl	24[b]	91	150–155 (0.5)	$C_{19}H_{29}NO$	79.39	79.48	10.17	10.17	4.87	4.32

[a] This amide was shown by its infrared spectrum to be contaminated with hexahydrobenzoic acid anhydride which was not removed by distillation. [b] Benzene was omitted from the reaction mixture; the pyridine solution was heated at 90° for 24 hr. [c] Recrystallization from cyclohexane. [d] The reaction was effected at room temperature. [e] Recrystallized from a mixture of ether and pentane. [f] M. Montagne and J. Puyal, *Anales Soc. Espan. Fis. Quim.*, **19**, 193 (1921); F. K. Beilstein, "Handbuch der organischen Chemie," Vol. IX, 2nd Suppl., 1920, p 7. [g] H. C. Brown, *J. Am. Chem. Soc.*, **60**, 1326 (1938). [h] A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

were converted to the corresponding hydroxides and subjected to the Hofmann elimination at pressures of 0.15 to 0.2 mm. The hydroxides decomposed at 65 to 80°. The neutral part of the product was quantitatively analyzed for *cis*- and *trans*-cyclooctenes by gas chromatography. The results are summarized in Table I. Cyclooctene was formed in moderately good yields (with a predominance of the *trans* isomer) when the other groups attached to the asymmetric nitrogen atom were aliphatic and contained β-hydrogen atoms which could compete in the Hofmann elimination. Attempts to reduce the effect of competing β-hydrogen atoms through the use of benzyl, allyl, and methallyl groups led to greatly reduced yields of cyclooctene in which the *cis* isomer predominated.

Experimental Section[6]

N-Benzylcyclooctylamine. A mixture of 126 g (1.00 mole) of cyclooctanone, 107.6 g (1.00 mole) of benzylamine, 0.5 g of *p*-toluenesulfonic acid monohydrate, and 150 ml of toluene was heated at the reflux temperature for 12 hr. The water formed during the reaction (18 ml) was collected by means of a Dean–Stark trap. Upon distillation, 203 g (95%) of N-benzylcyclooctanone imine, bp 139° (0.8 mm), was obtained.

A solution of 100 g of this imine in 400 ml of ethanol containing 2 g of prereduced platinum oxide was shaken with hydrogen at 30 to 40 psi. External cooling was required to keep the temperature below 50°. When the absorption of hydrogen had ceased, the solution was filtered, the filtrate was concentrated, and the residue was dissolved in 300 ml of 10% hydrochloric acid. This solution was washed with ether, and the product was liberated from the hydrochloric acid phase by the addition of solid sodium hydroxide and extraction with ether. The dried ether solution was concentrated and distilled giving 96 g (95%) of N-benzylcyclooctylamine, bp 120° (0.2 mm).

Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.17; N, 6.45. Found: C, 82.93; H, 10.50; N, 6.36.

N-Phenylcyclooctylamine. In a similar manner N-phenylcyclooctylamine, bp 132–142° (1.5 mm), was prepared in 89% over-all yield from cyclooctanone and aniline.

Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.62; H, 10.22; N, 6.86.

N-Isobutylcyclooctylamine, bp 72.0–72.5° (0.9 mm) [lit.[3] bp 72.0–72.5° (0.9 mm)], was prepared as described previously.[3]

N-Cyclooctylamides. The secondary amine to be acylated, a 1.5- to 2-fold excess of the appropriate acid chloride, and large excesses of pyridine and benzene were heated at the reflux temperature for 1 to 24 hr (see Table II). In two of the acylations with pivaloyl chloride, benzene was omitted, and the pyridine solution was warmed at 90° for 24 hr. The reaction of N-phenylcyclooctylamine with benzoyl chloride was effected at room temperature for 24 hr. All of the reaction mixtures were worked up as follows. The precipitated pyridine hydrochloride was separated by filtration, and the filtrate was concentrated. Equal amounts of benzene and water were added to the residue. The layers were separated and the organic layer was washed with 10% hydrochloric acid, 15% sodium hydroxide, and water. The benzene layer was dried with magnesium sulfate and concentrated; the residue was distilled or recrystallized. The physical properties and analyses of the amides thus prepared are given in Table II.

N,N-Disubstituted Cyclooctylamines 1–9. An ether solution of the amide to be reduced was slowly added to a stirred suspension of excess lithium aluminum hydride in ether. The resulting mixture was stirred at the reflux temperature for 1 to 84 hr (see Table III). The reaction mixture was worked up by a standard procedure[7] to give the amines **1–9** whose yields and properties are recorded in Table III.

N,N-Disubstituted Cyclooctylamines 10–14. A solution of equimolar quantities of the secondary amine, the alkylating agent (allyl bromide, methallyl bromide,[8] or ethyl-α-bromoacetate), and

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[6] Melting points were determined using a Kofler micro hot stage; melting points and boiling points are uncorrected. Analyses were performed by Dr. S. M. Nagy and associates and by Midwest Microlabs, Inc., Indianapolis, Ind.

[7] V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

[8] Methallyl bromide, bp 92.0–94.5°, was prepared by the procedure of W. J. Jones, S. T. Bowden, C. Edwards, V. E. Davis, and L. H. Thomas, *J. Chem. Soc.*, 1446 (1947).

Table III. N,N-Disubstituted Cyclooctylamines

Amine	R_1	R_2	Reaction time, hr	Yield, %	Bp (mm), or mp, °C	Formula	% C		% H		% N	
							Calcd	Found	Calcd	Found	Calcd	Found
1	Isobutyl	Ethyl	1	95	82.0–83.5 (0.75)	$C_{14}H_{29}N$	79.54	79.79	13.83	14.07	6.63	6.56
2	Isobutyl	*n*-Propyl	2	93	86.0–87.5 (0.22)	$C_{15}H_{31}N$	79.92	79.95	13.86	13.84	6.21	6.18
3	Isobutyl	Hexahydrobenzyl	18	64	126–128 (0.18)	$C_{19}H_{37}N$	81.64	81.53	13.34	13.40	5.01	5.23
4	Isobutyl	Neopentyl	84	80	91–93 (0.14)	$C_{17}H_{35}N$	80.55	80.53	13.92	14.10	5.53	5.60
5	Benzyl	Isobutyl	2	87	145–146 (0.5)	$C_{19}H_{31}N$	83.45	83.58	11.43	11.30	5.12	5.40
6	Benzyl	Neopentyl	18	84	125 (0.3)	$C_{20}H_{33}N$	83.56	83.59	11.57	11.52	4.87	4.91
7	Benzyl	β-Naphthyl	18[a]	85	80.5–81.0[b]	$C_{26}H_{31}N$	87.34	87.50	8.74	8.53	3.92	3.97
8	Phenyl	Benzyl	2	99	162 (1.0)	$C_{21}H_{27}N$	85.95	86.15	9.27	9.37	4.77	4.75
9	Phenyl	Neopentyl	2	92	125–130 (0.2)	$C_{19}H_{31}N$	83.45	83.61	11.43	11.53	5.12	5.09
10	Isobutyl	Allyl	9	40	72–73 (0.18)	$C_{15}H_{29}N$	80.64	80.95	13.09	13.03	6.27	6.00
11	Benzyl	$CH_2CO_2C_2H_5$	18	77	132.5–134.0 (0.13)	$C_{19}H_{29}NO_2$	75.20	75.30	9.53	9.35	4.62	4.84
12	Benzyl	Allyl	12	78	135 (0.3)	$C_{18}H_{27}N$	83.99	83.75	10.57	10.42		
13	Benzyl	Methallyl	12	87	134–135 (0.2)	$C_{19}H_{29}N$	84.07	83.84	10.77	10.77	5.16	5.16
14	Phenyl	Methallyl	12	84	132 (0.05)	$C_{18}H_{27}N$	83.99	83.67	10.57	10.38	5.44	5.42

[a] The reaction was effected at room temperature. [b] Recrystallized from hexane.

Table IV. Derivatives of N,N-Disubstituted Cyclooctylamines

Amine	R_1	R_2	Derivative	Mp, °C	Formula	% C		% H		% N	
						Calcd	Found	Calcd	Found	Calcd	Found
1	Isobutyl	Ethyl	Picrate[a]	91–92	$C_{20}H_{32}N_4O_7$	54.53	54.71	7.32	7.35	12.72	12.68
2	Isobutyl	*n*-Propyl	Hydrobromide[b]	162.0–163.5	$C_{13}H_{32}BrN$	58.81	59.00	10.53	10.73	4.57	4.76
3	Isobutyl	Hexahydrobenzyl	Picrate[a]	98–101	$C_{25}H_{40}N_4O_7$	59.04	58.82	7.93	7.98	11.02	10.99
4	Isobutyl	Neopentyl	Hydriodide[c]	180.0–182.5	$C_{17}H_{36}IN$	53.53	53.79	9.52	9.62	3.67	3.80
5	Benzyl	Isobutyl	Picrate[a]	117.5–120.0	$C_{25}H_{34}N_4O_7$	59.74	59.60	6.82	6.74	11.15	11.17
6	Benzyl	Neopentyl	Picrate[a]	144.5–146.0	$C_{26}H_{36}N_4O_7$	60.45	60.72	7.02	7.21	10.85	10.72
7	Benzyl	CH_2-β-$C_{10}H_7$	Picrate[a]	169–170	$C_{32}H_{34}N_4O_7$	65.51	65.62	5.84	6.01	9.55	9.62
8	Phenyl	Benzyl	Picrate[a]	161–162	$C_{27}H_{30}N_4O_7$	62.06	62.39	5.79	5.70	10.72	10.66
9	Phenyl	Neopentyl	Picrate[a]	150–152	$C_{25}H_{34}N_4O_7$	59.74	59.44	6.82	6.83	11.15	11.17
11	Benzyl	$CH_2CO_2C_2H_5$	Perchlorate[d]	205–207	$C_{19}H_{30}ClNO_6$	56.49	56.19	7.49	7.56	3.47	3.58
13	Benzyl	Methallyl	Picrate[a]	120–121	$C_{25}H_{32}N_4O_7$	59.99	60.19	6.44	6.77	11.19	11.18
14	Phenyl	Methallyl	Picrate[a]	132–134	$C_{24}H_{30}N_4O_7$	59.25	59.32	6.22	6.36	11.52	11.40

[a] Recrystallized from absolute ethanol. [b] Recrystallized from ethanol–tetrahydrofuran. [c] Recrystallized from methyl ethyl ketone. [d] Recrystallized from ether–acetonitrile.

sodium bicarbonate in absolute ethanol (about 1 mole of each reagent per liter of solvent) was heated at the reflux temperature for 12–18 hr. In the alkylations with allyl bromide, the mixture was warmed at 70° for 9–12 hr. The reaction mixture was filtered, and most of the ethanol was removed by evaporation. Ether was added and the resulting solution was extracted twice with water and dried with magnesium sulfate. Acetyl chloride was added to convert any unreacted secondary amine to the N,N-disubstituted acetamide. After 1 hr the mixture was extracted with 15% sodium hydroxide and with three portions of 10% hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide, and the tertiary amine was extracted with ether. The ether solution was dried with magnesium sulfate and distilled. The yields and properties of these amines are recorded in Table III.

When possible, the tertiary amines **1–14** were characterized as solid derivatives. The melting points and analyses of these derivatives are given in Table IV.

Methylations of the N,N-Disubstituted Cyclooctylamines. Procedure A. Amines **1** and **2** were dissolved in a large excess of methyl iodide; the solutions were kept at room temperature for 18 and 24 hr, respectively. After removal of the methyl iodide by evaporation, the residual methiodide was recrystallized several times from a mixture of acetone and ether. The methiodide of amine **1** was purified by fractional crystallization.

Procedure B. The amines were heated at the reflux temperature with excess methyl iodide in acetonitrile, ethanol, or methanol (see Table V). Amine **13** was heated at 50° for 60 hr with excess methyl iodide in methanol. The noncrystalline products were obtained by evaporation of the solvent at reduced pressure or by addition of a large volume of anhydrous ether. Trituration with anhydrous ether usually induced crystallization, and the methiodides were recrystallized from the solvents indicated in Table V. The methiodide of amine **3** was noncrystalline; it was stirred with 35% perchloric acid until the perchlorate crystallized. The quaternary ammonium perchlorate was purified and used for conversion to the hydroxide.

Procedure C. A mixture of 0.90 g (3.3 moles) of amine **12** and 1.5 g (8.1 mmoles) of methyl *p*-toluenesulfonate was placed in a thick-walled ampoule. The ampoule was evacuated to 0.05 mm, sealed, and heated at 80° for 48 hr. The reaction product was triturated with ether to induce crystallization and recrystallized from acetone.

The yields, melting points, and analytical data for the products of each of the above methylations are shown in Table V. The structures of these quaternary ammonium salts were confirmed by their infrared and nmr spectra.

N-Benzyl-N,N-dimethylcyclooctylammonium Iodide. This methiodide, mp 197°, was prepared from N-benzylcyclooctylamine by the exhaustive methylation procedure described previously.[9]

Hofmann Eliminations. Solutions of the quaternary ammonium hydroxides were prepared from about 12-mmole portions of the corresponding iodides by stirring them for 1 hr with an excess of silver oxide in aqueous ethanol solution and filtration of the resulting mixtures. The preparation of solutions of the quaternary ammonium hydroxides from the *p*-toluenesulfonate and the perchlorate was accomplished by elution through a column of Rexyn-RG-1(OH) ion-exchange resin[10] (quaternary ammonium type) with 50% aqueous methanol. Most of the solvent was removed with a rotary evaporator at 40° and 15–25 mm. The concentrates were then heated slowly to 65–80° at 0.15–0.20 mm until decomposition was complete. The distillate was collected in a trap cooled with Dry Ice. The products were washed from the Dry Ice trap and the distillation flask with pentane. The pentane solutions were

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(9) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger *J. Am. Chem. Soc.*, **82**, 4651 (1960).

(10) Fisher Scientific Co., Inc., Medford, Mass.

Table V. Quaternary Ammonium Salts of the Type $C_8H_{15}\overset{+}{N}R_1R_2CH_3X^-$

Starting amine	R_1	R_2	Procedure	Reaction time, hr	Yield, %	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
1	Isobutyl	Ethyl	A	18	74[a]	125–126	$C_{15}H_{32}IN$	50.98	51.17	9.13	9.09	3.96	3.88
2	Isobutyl	*n*-Propyl	A	24	87[a]	136.5–137.0	$C_{16}H_{34}IN$	52.31	52.08	9.33	9.09	3.81	3.81
3	Isobutyl	Hexahydrobenzyl	B[b,c]	72	92[a]	114.5–116.5	$C_{20}H_{40}ClNO_4$	60.97	61.21	10.23	10.24	3.56	3.66
5	Benzyl	Isobutyl	B[b]	26	71[a]	171.5–173.0	$C_{20}H_{34}IN$	57.82	57.64	8.25	8.19	3.37	3.49
10	Isobutyl	Allyl	B[d]	15	49[e]	106.0–107.5	$C_{16}H_{32}IN$	52.60	52.38	8.83	9.00	3.83	3.78
12	Benzyl	Allyl	B[f]	60	64[g]	154.0–154.5	$C_{19}H_{30}IN$	57.14	56.90	7.57	7.60	3.51	3.57
13	Benzyl	Methallyl	C	48	85[h]	127–129	$C_{27}H_{40}NO_3S$	70.70	70.88	8.79	8.59	3.05	2.92

[a] Recrystallized from a mixture of acetone and ether. [b] The solvent used in the reaction was acetonitrile. [c] The quaternary ammonium perchlorate was isolated and characterized. [d] The solvent used in the reaction was ethanol. [e] Recrystallized from a mixture of acetone and tetrahydrofuran. [f] The solvent used in the reaction was methanol. [g] Recrystallized from acetone containing a little ethanol. [h] Recrystallized from acetone.

extracted twice with 10% hydrochloric acid and dried with magnesium sulfate. A known amount of *cis,cis*-1,5-cyclooctadiene was added as an internal standard, and the pentane solutions were subjected to gas chromatography on an 8-ft by 0.25-in. column of 4-methyl-4-nitropimelonitrile (NMPN) at 65°. The amounts of *cis*- and *trans*-cyclooctenes were calculated by comparison of the resulting chromatogram with chromatograms of solutions containing known amounts of *cis*- and *trans*-cyclooctenes and *cis,cis*-1,5-cyclooctadiene.

Attempted Methylation of N-Benzyl-N-neopentylcyclooctylamine. A. N-Benzyl-N-neopentylcyclooctylamine (5 g) was dissolved in 1 to 2 ml of methanol and treated with methyl iodide until a homogeneous solution resulted (about 5 ml). The mixture was kept at 70° for 12 hr; the excess methyl iodide and methanol were removed at reduced pressure. The residue was extracted several times with ether or pentane and then recrystallized from methanol–ether, mp 165–176°. The melting point and infrared spectrum of the product were identical with that of a sample of N-benzyl-N-neopentylcyclooctylammonium hydriodide prepared by treatment of the tertiary amine with a 55% solution of hydriodic acid followed by recrystallization from acetone–ether.

Anal. Calcd for $C_{20}H_{34}IN$: C, 57.83; H, 8.25; I, 30.55; N, 3.37. Found: C, 57.52; H, 8.03; I, 30.86; N, 3.65.

B. N-Benzyl-N-neopentylcyclooctylamine (3.0 g) was dissolved in 6 ml of methyl iodide, sealed in an ampoule, and heated at 150° for 24 hr. Extraction with ether and removal of the solvent afforded a yellow-brown oil which after recrystallization from methanol–ether and acetone–ether had mp 197°. The product was identified by its infrared spectrum and elemental composition as N-benzyl-N,N-dimethylcyclooctylammonium iodide. An authentic sample of the quaternary salt was synthesized independently from N-benzylcyclooctylamine according to a procedure previously described,[9] and the two samples were identical.

Anal. Calcd for $C_{17}H_{28}IN$: C, 54.69; H, 7.56; N, 3.75. Found: C, 54.63; H, 7.53; N, 3.90.

Attempted Methylation of N-Benzyl-N-phenylcyclooctylamine (8). A 5-g sample of the amine **8** was treated with 5 ml of methyl iodide in 3 ml of methanol. The mixture was heated to the reflux temperature for 72 hr. After removal of excess solvent with a rotary evaporator, ether was added to the residue. Two recrystallizations of the insoluble material from acetone containing a small amount of ether afforded 1.4 g of needle-like crystals, mp 138.0–138.5° dec. The infrared spectrum showed an absorption in the 2500-cm^{-1} region characteristic of $^{+}$N–H. Treatment of the product with base, extraction with ether, and distillation afforded the starting amine, bp 170–185° (0.7 mm); $n^{25.5}D$ 1.5913.

Anal. Calcd for $C_{21}H_{28}IN$: C, 59.86; H, 6.70; I, 30.12; N, 3.32. Found: C, 60.27; H, 6.77; I, 29.31; N, 3.00.

An authentic sample of N-benzyl-N-phenylcyclooctylammonium iodide was prepared by trituration of the tertiary amine with 1 to 2 ml of 57% hydriodic acid in the cold. The yellow crystals were dissolved in methanol, ether was added, and the mixture was cooled to 0° for crystallization. After two recrystallizations from methanol–ether, the product had mp 141.0–141.5°. A mixture melting point with the product obtained from attempted methylation showed no depression.